Design of Clinical Trials in AKI: A Report from an NIDDK Workshop. Trials of Patients with Sepsis and in Selected Hospital Settings


Summary
AKI remains an important clinical problem, with a high mortality rate, increasing incidence, and no Food and Drug Administration-approved therapeutics. Advances in addressing this clinical need require approaches for rapid diagnosis and stratification of injury, development of therapeutic agents based on precise understanding of key pathophysiological events, and implementation of well designed clinical trials. In the near future, AKI biomarkers may facilitate trial design. To address these issues, the National Institute of Diabetes and Digestive and Kidney Diseases sponsored a meeting, “Clinical Trials in Acute Kidney Injury: Current Opportunities and Barriers,” in December of 2010 that brought together academic investigators, industry partners, and representatives from the National Institutes of Health and the Food and Drug Administration. Important issues in the design of clinical trials for interventions in AKI in patients with sepsis or AKI in the setting of critical illness after surgery or trauma were discussed. The sepsis working group discussed use of severity of illness scores and focus on patients with specific etiologies to enhance homogeneity of trial participants. The group also discussed endpoints congruent with those endpoints used in critical care studies. The second workgroup emphasized difficulties in obtaining consent before admission and collaboration among interdisciplinary healthcare groups. Despite the difficult trial design issues, these clinical situations represent a clinical opportunity because of the high event rates, severity of AKI, and poor outcomes. The groups considered trial design issues and discussed advantages and disadvantages of several short- and long-term primary endpoints in these patients.


Introduction
Successful therapeutic interventions in the treatment of AKI remain an important clinical opportunity, because there are no therapeutic agents approved by the Food and Drug Administration. Past clinical studies have been hampered by delayed diagnosis (1), late administration of drugs, lack of stratification by degree of injury (2), low statistical power, and adverse medication side effects. These substantial clinical barriers prompted the National Institute of Diabetes and Digestive and Kidney Diseases-sponsored meeting “Clinical Trials in Acute Kidney Injury: Current Opportunities and Barriers” held December 2 and 3, 2010, on the National Institutes of Health campus that included academic investigators, industry partners, and representatives from the NIH and the Food and Drug Administration to address this problem in a multidisciplinary fashion. Two working groups convened and addressed key questions pertaining to the design of AKI clinical trials. Discussions were focused on two clinical settings in which AKI occurs to provide meaningful and specific trial design information. Clinical trial design issues focused on prevention and treatment of sepsis-associated AKI (SA-AKI) and critical care-associated AKI. Variability in risk, potential response to interventions, and presentations in these settings will pose challenges in trial design. It was also recognized and discussed that overlap of the patient populations likely occurs in these settings and will increase heterogeneity.

Sepsis
Moderators: Dr. Lakhmir S. Chawla and Dr. James S. Kaufman
Sepsis and septic shock are important causes of AKI in critical care units. They occur in more than one-half of the cases in the intensive care unit (ICU) and are associated with high mortality rates (3,4). In designing an interventional study for SA-AKI, we considered phases of injury and pathophysiologic mechanisms, despite our incomplete knowledge of these processes. Multiple injury pathways have been shown to be involved in SA-AKI (5–7). Therefore, any interventional
study of SA-AKI must include the treatment of sepsis itself and issues of volume resuscitation. Appropriate study populations and interventions will depend on the phase of injury. Furthermore, large sample sizes are required to conduct sepsis studies, in part because of the heterogeneity of both causes of sepsis and the patient population.

**What Are the Characteristics of Patients Who Should Be Selected for SA-AKI Trials?** Three strategies for patient selection are proposed to minimize the heterogeneity typically associated with an SA-AKI trial. First, use of a severity of illness score (e.g., Acute Physiology, Age, Chronic Health Evaluation [APACHE]) excludes patients that are so severely ill that no effective intervention would be expected. Second, targeting a particular etiology of sepsis decreases the overall heterogeneity (e.g., pneumonia or intra-abdominal sepsis). This approach would have the advantage of reducing the heterogeneity by narrowing the types of causative organisms, timing, and disease pathogenesis. Patients with pneumonia and sepsis were identified as particularly suitable study populations, because pneumonia is a common cause of SA-AKI; also, ventilator requirements and severity of comorbidities may be less variable than in other populations (4). Third, because SA-AKI is often accompanied by cardiovascular and respiratory organ failure (8), patients with this combination represent a relatively homogenous population of SA-AKI compared with patients with all forms of SA-AKI. However, these patients are likely to have established and/or multifactorial SA-AKI and therefore, might be less able to respond to a targeted therapeutic intervention.

The shortcomings in our understanding of the pathophysiology of SA-AKI may preclude isolating a single biologic target for intervention. Nevertheless, there are several guiding principles. First, any treatment for SA-AKI should ameliorate sepsis in general, decreasing both SA-AKI and overall mortality. Second, interventions for SA-AKI should be congruent with the Risk, Injury, Failure, Loss of function, and End-stage Renal Disease (RIFLE) stage of SA-AKI. For instance, early interventions during RIFLE R (Risk) or I (Injury) stages for SA-AKI should be focused on mechanisms that restore or protect kidney function. Interventions during RIFLE F (Failure) stages could be focused on renal supportive interventions (e.g., continuous renal replacement therapy or management of volume overload), hastening repair or reducing chronic injury or structural changes such as fibrosis. Third, interventions should attenuate the systemic manifestations of AKI. Preclinical data endorse the notion that kidney injury itself has a negative impact on other organs, particularly the lung (9). In addition, critically ill patients with AKI requiring dialysis have worse outcomes compared with APACHE score-matched patients with ESRD (10). These data suggest that, if the acute effects of AKI could be modulated, secondary distant organ injury or dysfunction might be attenuated.

**What Should the Primary and Secondary Study Outcomes Be in SA-AKI Trials, and What Are the Most Appropriate Data Sources to Inform Planning?** Endpoints for studies in patients with SA-AKI should be consistent with previously established endpoints in sepsis studies. Primary short-term endpoints could include death, and the composite of death and the adjudicated need for acute dialysis at 28 days. A longer-term endpoint could include adjudicated need for acute dialysis at 90 days. Because of variability in initiation of renal replacement therapy (both across sites and across providers within sites), adjudicated criteria for initiation of dialysis based on severity and complications are essential, even if it is not offered to patients or if they decline dialysis because of futility considerations. In addition, because AKI has been shown to increase the risk for future decline in kidney function, endpoints at time periods longer than 90 days could include progression to advanced CKD (11). Important for this determination is an understanding of the patients’ preinjury or baseline kidney function. Expanded composite endpoints that would be appropriate in phase 2 studies include death, the adjudicated need for acute dialysis, and doubling of baseline serum creatinine concentration (SCr). Death and dialysis are competing risks, because patients who die will not progress to need dialysis. Composite endpoints in which the outcomes of death, adjudicated need for acute dialysis, and changes in SCr are ranked for statistical analysis may be useful. Potential short-term endpoints during the acute hospitalization phase that should be assessed include degree of fluid overload, dialysis- and ventilator-free days, and improvement or worsening of AKI Network stage. AKI biomarkers, at this point in time, were specifically not thought suitable as short-term endpoints because of their current uncertain relationship to hard clinical endpoints. AKI biomarkers, however, should be measured in any SA-AKI clinical trial to determine their potential relevance as surrogate outcome measures for designing future studies. In addition, it was felt that the current Sequential Organ Failure Assessment (SOFA) score, commonly used in the assessment of illness severity in studies of sepsis, may be overly sensitive to the presence of CKD. However, the compatibility of renal SOFA and the sepsis organ failure scoring in conjunction with AKI Network staging should be established. This establishment would require interdisciplinary cooperation. Trial design should incorporate the estimation of event rates for these varied outcomes.

**Summary**

A trial in patients with sepsis and AKI or at risk of developing AKI should minimize the heterogeneity of the patient population through targeting an intermediate severity of illness and a particular etiology of sepsis. Therapies considered should not only attenuate kidney injury but reduce morbidity and mortality. Primary endpoints could include death, and the composite of death and the adjudicated need for acute dialysis at 28 and 90 days or even greater time periods for longer-term endpoints. Expanded composite endpoints that would be appropriate might also include a doubling of SCr at 90 days. AKI biomarkers should be measured to establish their relevance as surrogate outcome measures, but at this time, their use as endpoints is premature.

**Trauma/Surgery/ICU**

**Moderators: Dr. Prasad Devarajan, Dr. Robert M. Toto, and Dr. Chi-yuan Hsu**

Clinical studies focused on the trauma, postoperative, and ICU populations are important because of the high
event rate, severity of AKI, and poor outcomes. Successful intervention in this population could have a high impact, because the mortality can reach 50%–60% of patients, especially in those patients receiving ICU care (3,12,13).

How Should Priorities Be Set for Choosing Interventional Strategies in Studies of Patients with Trauma/Postoperative/ICU AKI? Both process and patient characteristics play roles in choosing patients to enroll in AKI interventional trials. Process factors include awareness on the part of surgeons and intensivists that a study is taking place and willingness of these physicians to give investigators notification that a patient is at risk for AKI and could be eligible for a trial. ICU care providers need to be educated about trials in progress and the procedures for getting a patient into a trial. As a practical matter, obtaining informed consent, either from the patient or a surrogate, is crucial.

The challenge of obtaining informed consent is formidable and a major obstacle to conducting trials in the ICU. Early in the planning stages of a trial, close communication and productive collaborations should be established between the trialists and attending surgeons and intensivists in charge of the care of such patients. The nature of the exposure (e.g., rhabdomyolysis, shock, sepsis, or contrast) may determine whether a patient is eligible for a trial. Patient factors that pose challenges relate to timing after exposure and the nature of the exposure. Some patients are at risk of early AKI, for example, after shock resuscitation, whereas others are at risk of developing AKI later in an ICU stay. The ability to readily obtain informed consent from a family member is an ideal characteristic given the challenges in obtaining consent in this setting.

What Should the Timeframes Be for Short- and Long-Term Outcomes in Interventional Trials of Trauma/Postoperative/ICU AKI Patients? How Should the Timeframes Be Determined? Studies using short- and long-term outcomes provide different information. A 28-day timeframe (short term) may be appropriate for assessing safety and effectiveness of an intervention and providing data regarding mortality and need for dialysis, whereas a 90-day timeframe (long term) would be appropriate for assessing development of CKD. In addition, assessment of residual kidney function 6 and 12 months after AKI may be desirable for confirming the presence of CKD and assessing a patient’s overall functional status (11,14–19), although intervening events may cloud the picture during this timeframe.

What Are the Expected Rates of Adverse Events and Serious Adverse Events in Patients with Trauma/Postoperative/ICU AKI Who Might Be Selected for Interventional Trials? What Are the Data Sources that Can Be Used for Planning Purposes? The expected rates of adverse events in this population are high (20), but the precise rates are uncertain and likely to change over time. Because these patients are severely ill with multiple medical problems, distinguishing adverse events attributable to an intervention from events unrelated to the intervention may be difficult. Relatively mild adverse events (e.g., a small increase or decrease in BP) that would be important in an outpatient study may not even be detectable in ICU patients because of the severity and complexity of their illnesses.

Short-term parameters such as AKI scoring system results can be used to stratify maximal AKI severity, even if they are not associated with hard outcomes. Obtaining baseline data, for example, from trauma and ICU registries is important, because this information would enable prediction of the likelihood of an event in the absence of AKI-specific therapy. This likelihood can be compared with the frequency of events in trial participants. Data sources that can be used for planning purposes include trauma registries, the Program to Improve Care in Acute Renal Disease study, the University of California at San Diego/University of Alabama at Birmingham O’Brien registry, and Health Maintenance Organization and Veterans Affairs databases. These estimates will help to design phase 2 therapeutic trials to further establish a baseline for use in subsequent trials.

What Are the Considerations that Should Be Taken into Account in Considering Patients with Trauma/Postoperative/ICU AKI? How Will Assessments Differ in Pilot/Feasibility Versus Definitive Outcome Studies for Interventions in this Patient Population? The opportunities and barriers in the context of studying these patient populations may differ considerably from most other clinical settings. The benefits of choosing the trauma/postoperative/ICU population for study are the high rate and severity of AKI in this population (20). The barriers include the heterogeneity of the patient population, the difficulty in obtaining consent, and the likelihood that these patients might be recruited for competing studies on other topics.

It is important to understand the high risk and heterogeneity of the patient population. The age range of the population is wide, and nearly all are exposed to multiple medications, including nephrotoxic agents (nephrotoxic antibiotics and radiocontrast agents). Many are hypotensive or have experienced significant periods of hypotension. Many develop sepsis, and intravascular volume depletion is common in the preoperative period or after sustaining trauma.

Assessment in pilot/feasibility studies would focus primarily on short-term outcomes (such as in-hospital mortality, adjudicated requirement for acute dialysis, and changes in SCR). Assessments for definitive studies should include the short-term outcomes mentioned above as well as long-term outcomes (CKD stage, quality of life, development of cardiovascular disease, and mortality) (21).

What Are the Ideal Characteristics of Patients Who Could Be Selected for Interventional Trials in Patients with Trauma/Postoperative/ICU AKI? The ideal characteristics of these patient populations depend on the phase and goals of an intervention study. In general, those patients who are likely to respond to the intervention and survive for the duration of the study are critical to trial success. These patients would have neither a maximal risk (low likelihood of survival long enough to obtain meaningful results) nor a minimal risk (because of the likelihood that interventions will not make a meaningful difference in their outcome). Stratification of the level of kidney injury at the beginning of the trial would help with appropriate patient assignment.

What Should the Primary and Secondary Study Outcomes Be in Interventional Trials of Trauma/Postoperative/ICU AKI Patients, and What Are the Most Appropriate Data Sources for Trial Planning? Studies using short- and long-term outcomes provide different information.
A 28-day timeframe (short term) may be appropriate for assessing safety and effectiveness of an intervention and providing data regarding mortality and need for dialysis, whereas a 90-day timeframe (long term) would be appropriate for assessing development of CKD. In addition, assessment of residual kidney function 3, 6, and 12 months after AKI may be desirable for confirming the presence of CKD and assessing a patient’s overall functional status.

Primary short-term endpoints include 28-day survival, adjudicated need for in-hospital renal replacement therapy, and worsening of kidney function. Secondary endpoints could include duration of ICU stay, total length of hospital stay, number of ventilator-dependent days, and dependence on dialysis at hospital discharge.

Longer-term (months to years) endpoints include the development and stage of CKD and health-related quality of life (HRQOL), including such factors as the need for long-term skilled care and/or dialysis dependence (11,22,23). Hospital discharge may not be informative, because patients may be discharged from a hospital but spend the remainder of their lives (months or years) in a skilled nursing facility. Discharging patients home may be a more meaningful outcome. Yearly SCR measurements for 3 or 4 years could provide valuable information on the natural history of kidney function. Current NIH-funded studies have included follow-up assessments of kidney function for 2 or 3 years but not for longer periods. However, long-term studies have shown an increased risk for mortality, development of CKD, and progression of ESRD after an episode of AKI requiring dialysis in numerous clinical situations (17,24,25).

Assessment of HRQOL entails using difficult variables, because they may not be directly related to kidney function. For example, for a patient who experienced AKI and also had an amputation, the amputation may be the key factor in subsequent assessment of HRQOL. These patients are complicated with multiple problems, and it is difficult to determine the extent, if any, to which AKI contributes to other outcomes.

Other long-term outcomes to be considered for inclusion are mortality, cardiovascular events, and rate of rehospitalization (22,26).

What Are the Potential Biomarkers and Surrogate Outcomes to Be Used in Studies of Interventional Strategies in Patients with Trauma/Postoperative/ICU AKI? The biology of candidate structural injury biomarkers is not well understood. Work is in progress, but these novel biomarkers, in general, have not been validated for initiation of clinical trials in AKI in these patient populations (23); they may be of limited use, because the patients are often very unstable.

Potentially useful surrogate outcomes include SCR, other biomarkers, and measurements of GFR. Examination of these biomarkers could be important for a better understanding of their potential role in guiding future clinical trials and to serve in predictive modes. Biomarkers should be assessed prospectively in clinical trials to better understand their use and limitations in these settings.

How Should Stopping Guidelines Be Used in Interventional Studies in Trauma/Surgery/ICU AKI Patients? Safety signals as stopping guidelines are important for every trial phase. Efficacy signals are important in phase 2 and beyond. Signals would be determined in early studies of the agent for use in later trials, and they must be informed and guided by the morbidity of the underlying population. In general, phase 2 trials should not be stopped because of efficacy, because this could lead to a failure to detect important events that might occur later in the trial. Stopping a trial for lack of efficacy would be appropriate in phase 2 studies. In contrast, stopping a trial because clinical efficacy has been shown may be appropriate in phase 3 studies. In either case, statistically rigorous, prespecified stopping rules are required. Because actual event rates are often lower that those rates predicted before trial initiation, the use of adaptive study designs, which provide for adjustment in sample size based on prespecified interim assessments of endpoint rates (27), might be particularly useful to prevent ending up with an underpowered study.

Summary

Trauma, postoperative, and ICU populations are valuable to study because of the high event rate and severity of AKI. Short-term primary endpoints in these patient populations should include 28-day survival, in-hospital dialysis requirement, and worsening of kidney function. In long-term studies, CKD staging and HRQOL are important endpoints. Potential surrogate outcomes in interventional studies in this patient population include markers of filtration such as SCR, measurements of GFR, and other biomarkers of structural kidney injury. The expected rate of serious adverse events in this patient population is high but unknown. However, several data sources are available for planning purposes. These sources include trauma registries, the Program to Improve Care in Acute Renal Disease study, the University of California at San Diego/University of Alabama at Birmingham O’Brien registry, and Health Maintenance Organization and Veterans Affairs databases. Stopping guidelines for trials in this population include safety and efficacy signals, and they must be informed by the morbidity of the underlying population and be statistically rigorous.

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Disclosures

None.

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